

Management of locally advanced breast cancer

Locally advanced breast cancer refers to clinical stage 3 disease.

ELIZABETH MURRAY, MMed Rad CT, FCRad Onc

Principal Consultant, Clinical Radiation Oncology, Groote Schuur Hospital and University of Cape Town

Elizabeth Murray is member of the Scientific Committee of the International Breast Cancer Study Group and a member of the Early Breast Cancer Trialists' Collaborative Group.

For the purposes of this article 'locally advanced breast cancer' refers to clinical stage 3 disease which may include involvement of supraclavicular nodes (Table I). The postoperative treatment of T1 - 2 tumours which are found to be pathologically stage 3 due to 4 or more nodes being involved with cancer, will be covered elsewhere.

Table I. Stage 3 disease

T3N1: Tumour >5 cm with clinically detectable mobile axillary nodes
T4 any N: Tumour of any size with direct extension to
a. chest wall
b. skin, provided this is oedema, satellite nodules confined to the breast or ulceration
c. both a & b or
d. inflammatory
Any T, N2 or 3: Tumour of any size with fixed or matted axillary nodes and/or ipsilateral internal mammary metastases and /or supraclavicular metastases

**In developing countries
50 - 80% of breast cancer
patients present at
advanced stage.**

In developing countries 50 - 80% of breast cancer patients present at advanced stage.^{1,2} In Cape Town, 30% of patients in state hospitals present with stage 3 disease. In mammographically screened populations this figure is probably <5%.³

The clinical diagnosis of stage 3 breast cancer is often obvious, but delay in diagnosis may occur in certain cases, for example in inflammatory breast cancer which can mimic cellulitis, and in pregnancy.

For staging tests in stage 3 disease, see Table II. Blood tumour markers may also be used but do not form an essential part of diagnosis or monitoring.

Table II. Screening tests

Chest X-ray
Liver ultrasound
Bone scan
Full blood count, liver function tests and calcium
Ultrasound liver and/or CT scan liver/chest*

* If indicated.

Treatment approaches

The use of an interdisciplinary clinic is highly recommended.

The triple modality approach

Combined modality treatment using chemotherapy, surgery and radiotherapy is regarded as preferred treatment.^{3,4} Hormone therapy is added if receptors are positive, and today biological therapy where appropriate and affordable. Although results of phase 3 studies testing the multimodality approach are generally not available, results overall have suggested better survival with this approach, with local recurrence rates of approximately 20% or less and 5-year survival figures of approximately 50% (range 20 - 85%) reported³ (prior to the development of biologicals). This conventional approach has been found to be particularly effective in inflammatory breast cancer.⁵

**A typical regimen used in
the resource-limited public
sector in South Africa
would be one incorporating
cyclophosphamide,
adriamycin and
5-fluorouracil.**

Chemotherapy and biological treatment

Chemotherapy may be given pre- and/or postoperatively. In inflammatory disease preoperative chemotherapy is standard. Advantages of giving chemotherapy preoperatively include 'downstaging' (although actual stage grouping always remains the same), which will allow surgery in initially inoperable cases or may even allow breast-conserving therapy. The effects of chemotherapy can be monitored with ineffective treatment being discontinued. Response rates are traditionally 60 - 80% with pathological complete response <10%, but better responses are seen with newer agents. A typical regimen used in the resource-limited public sector in South Africa would be one incorporating cyclophosphamide, adriamycin and 5-fluorouracil. In the private sector a taxane is likely to form part of the regimen.

Neoadjuvant trastuzumab in Her2-positive patients more than doubled the pathological complete response rate in the Neoadjuvant Herceptin (NOAH) Phase III study (Besalga ECCO meeting 2007).

In inflammatory disease preoperative chemotherapy is standard.

Surgery

Mastectomy is usually the mainstay of surgical treatment in stage 3 disease but the extent of surgery thought appropriate may vary from surgeon to surgeon, with some having a more conservative approach and others advocating resection of extensive disease with fascia and muscle and a latissimus dorsi flap.

Immediate or delayed reconstruction can be considered, although the cosmetic outcome may be affected by radiotherapy. Certain tumours may be suitable for breast-conserving surgery after chemotherapy.

Radiotherapy

Radiotherapy generally follows chemotherapy and surgery. It results in a reduction of locoregional recurrence of about two-thirds and also has been shown to improve survival in high-risk and node-positive disease,⁶⁻⁹ although a consistent survival benefit in stage 3 disease has not been shown.¹⁰ In stage 3, radiotherapy usually includes treatment of at least the chest wall and supraclavicular fields. Internal mammary nodes are commonly treated, but axillary treatment is usually avoided because of the risk of brachial plexopathy. Other serious complications include small risks of cardiac damage and lung and opposite breast cancers. Treatment usually lasts for 5 weeks and is generally well tolerated.

Hormonal treatment

In patients with positive hormone receptors, hormonal treatment will be added. In premenopausal patients this may be

tamoxifen and in postmenopausal women aromatase inhibitors will be incorporated where affordable. This will be done either immediately, or after 2 - 3 years of tamoxifen or as extension therapy after 5 years of tamoxifen. The exact role of ovarian function suppression (GnRH analogue or oophorectomy) in premenopausal women is still under study.

Neoadjuvant endocrine therapy

This has not yet become a standard treatment, but in certain patients it may be appropriate and is followed by surgery.

Sequential approach

This approach starts with hormonal therapy and uses other treatments as necessary. This may be a reasonable option for managing locally advanced disease in certain hormone receptor-positive patients^{11,12} but is generally confined to less fit, older patients or those who decline a more conventional treatment approach.

Radiotherapy in inoperable disease

As well as being used postoperatively, radiotherapy is used if the disease remains inoperable after systemic treatment or if surgery is refused. Radiotherapy alone does not lead to good control rates.³ It provides some loco-regional control, protecting against¹³ or treating ulceration, haemorrhage and malignant brachial plexopathy. The high doses usually necessary to achieve good local control rates have significant rates of necrosis and severe fibrosis. Neutron radiotherapy may provide a useful short course with reasonable local control rates.

References

1. Murray E. The management of breast cancer in Africa. A review of the problems presented by breast cancer in Africa. In: Ly A, Khayat D, eds. *About Cancer in Africa*, 1st ed. Paris: Springer, 2006: 27-41.
2. Carlson RW, Anderson BO, Chopra R, et al. Treatment of breast cancer in countries with limited resources. *The Breast Journal* 2003; 9(Suppl.2): S67-S74.

3. Hortobagyi GN, Singletary SE, Strom EA. Treatment of locally advanced and inflammatory breast cancer. In: Harris JR, Lippman ME, Morrow M, eds. *Diseases of the Breast*, 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 2000: 645-660.
4. Murray EM. Medical and radiation oncology for breast cancer in developing countries with particular reference to locally advanced breast cancer. *World J Surg* 2003; 27: 924-927.
5. Hortobagyi GN. Multi-disciplinary management of advanced primary and metastatic breast cancer. *Cancer* 1994; 74: 416-423.
6. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. *Lancet* 2000; 355: 1747-1770.
7. Harris JR, Halpin-Murphy P, McNeese M, et al. Consensus statement in postmastectomy radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; 44: 989-990.
8. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; 337: 956-962.
9. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997; 337: 949-955.
10. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19: 1539-1569.
11. Tan SM, Cheung KI, Willsher PC, et al. Locally advanced primary breast cancer medium-term results of a randomized trial of multimodal therapy versus initial hormone therapy. *Eur J Cancer* 2001; 37: 2331-2338.
12. Willsher PC, Robertson JFR, Chan SY, et al. Locally advanced breast cancer: early results of a randomized trial of multimodal therapy versus initial hormone therapy. *Eur J Cancer* 1997; 33: 45-49.
13. Yarnold J. Radiation in the context of multidisciplinary approaches: locally advanced disease. *The Breast* 2000; 10: S8.

Acknowledgement

Extensive use has been made of refs 1 and 4, ref. 4 with kind permission of Springer Science and Business Media.

In a nutshell

- The choice of treatment approach must be tailored not only to the type of tumour and its receptors but also to the patient's general medical condition, socio-economic circumstances and wishes.
- Patients are followed up for disease relapse and assisted to regain their places as well-functioning members of society.
- The first step tackling of the problem of locally advanced breast cancer is to improve awareness of breast problems among women and their doctors so that presentation at this stage is prevented.